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Human *Cytomegalovirus* Infection of a Severe-Burn Patient: Evidence for Productive Self-Limited Viral Replication in Blood and Lung

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To date, only seroepidemiological data are available on the role of human cytomegalovirus (HCMV) in patients with severe burns. We present the first longitudinal analysis of disseminated HCMV infection with a demonstration of self-limited productive viral replication identified in both the blood and lung of a burn patient.

CASE REPORT

An otherwise-healthy, 40-year-old female presented to our burn center after having suffered a 65% total body-surface-area self-immolation burn. She sustained full-thickness burns to her neck, both her arms, her chest, her abdomen, and her back as well as partial-thickness burns to both upper and lower extremities. On postburn day 2, a tracheostomy was performed. Subsequently, a fascial excision of all of the full-thickness-burned area was performed, and the area was covered with glycerol-preserved allogeneic skin (Euroskin; Beverwijk, The Netherlands). After removal of the cadaver skin, meshed split-thickness autologous skin was transplanted to both the arms and the neck. On hospital day 23, after the removal of the cadaver skin from the patient's chest and abdomen and the debrided areas on both legs, these areas were grafted with cultured epithelial autografts (Epicel; Genzyme Tissue Repair, Cambridge, MA) simultaneously overlaid on acellular allogeneic dermis (AlloDerm; LifeCell Corp., Branchburg, NJ). The back was grafted with split-thickness autologous micrografts (1:6; Meek) simultaneously overlaid on Alloderm. All areas of the skin transplants healed uneventfully, with the exception of the back. The transplanted area on the back developed a heavy bacterial colonization with pus and partial graft loss 10 days after transplantation (postburn day 56). Wound swabs revealed *Staphylococcus epidermidis* and *Staphylococcus aureus*, while blood cultures stayed negative for bacterial pathogens. As a result of wound care and intravenous antibiotics, wound healing without sequelae was observed within 2 days. During the course of the intensive care unit stay, the patient suffered from multiple septic episodes (3) with body temperatures of >38°C or <36°C, tachycardia of >90 beats/min, tachypnea or a need for mechanical ventilation, and leukocytosis of $>12 \times 10^3$ cells/mm^3 or $<4 \times 10^3$ cells/mm^3 (3). Daily chest X rays excluded any radiological evidence of interstitial pneumonia. Within the first 3 weeks after the burn, the patient received 32 units of packed red blood cells. The patient was weaned from the ventilator on hospitalization day 77 and discharged from the intensive care unit 4.5 months after the injury.

Longitudinal human cytomegalovirus (HCMV) screening was performed using serology, virus culturing, and nucleic acid amplification techniques from day 0 to day 120 after the burn (Fig. 1). Serology was done by anti-HCMV immunoglobulin G (IgG)/IgM enzyme-linked immunosorbent assay (DiaSorin, Düsseldorf, Germany). Virus culturing was performed by conventional tube cell culturing of bronchoalveolar lavage (BAL) fluids, throat swabs, urine samples, and skin biopsy specimens. Nested PCR with leukocytes, plasma, BAL fluids, throat swabs, and skin biopsy specimens was performed using primer sequences from the HCMV immediate-early region exon 4 (8). Quantitative HCMV DNA was detected with a COBAS AMPLICOR CMV MONITOR test (Roche Diagnostics), and qualitative HCMV late pp67 mRNA was screened by nucleic acid sequence-based amplification (Organon Teknika, Boxtel, The Netherlands) (5) from blood and BAL fluids.

The initial serostatus of the patient was unknown. On day 0, HCMV DNA was not detectable in serum. Fluctuating HCMV IgG levels resulted from the transfusion of multiple blood products. HCMV IgM seroconversion was initially observed on postburn day 25, when the patient was septic (3). The patient suffered from disseminated HCMV infection with viral leukocyte and plasma DNAemia. The peak level of the viral load was noted on postburn day 39 and was greater than 10,000 copies of HCMV DNA/ml plasma. Viral replication in blood was productive from day 21 to day 45 after the burn, as confirmed by the simultaneous detection of late viral RNA (Fig. 1). Low viral DNA levels were detectable in plasma for an additional week. The retrospectively analyzed course of the plasma viral DNA load described a unimodal kinetics (Fig. 1). Antiviral treatment was not performed. Despite the lack of radiological signs of interstitial pneumonia, both viral DNA and late viral RNA were detectable simultaneously in BAL fluids. Additionally, viral isolates from BAL fluids and viral DNA from throat swabs were also obtained during this time. Interestingly, productive viral replication in the lung seemed to persist for nearly

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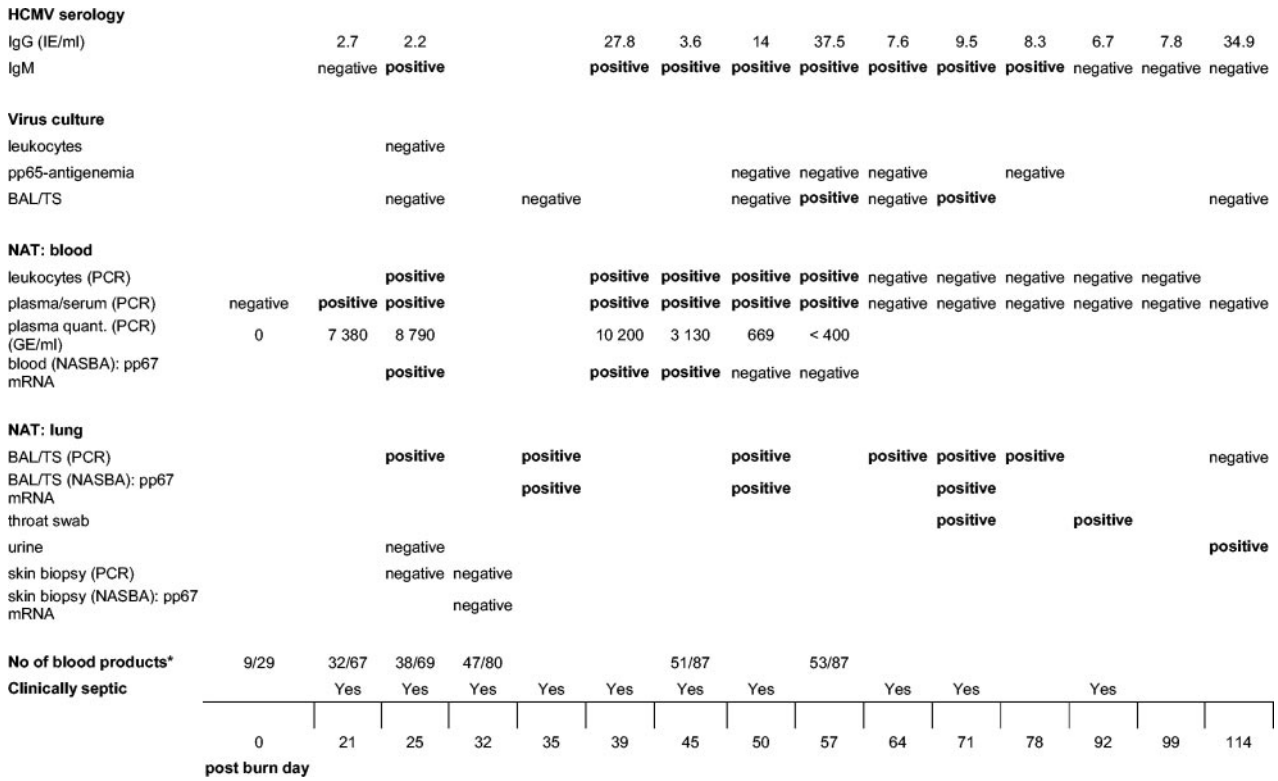

FIG. 1. Synopsis of longitudinal HCMV screening of a severe-burn patient. *, the cumulative numbers of transfused blood products (packed red cells versus fresh frozen plasma) are given. NAT, nucleic acid amplification techniques; TS, throat swabs; GE, genome equivalents; NASBA, nucleic acid sequence-based amplification.

1 month longer than observed in the blood. Therefore, viral RNA and infectious virus could be isolated from BAL fluids as late as postburn day 71 (Fig. 1).

Very little data are available on the role of HCMV as an etiological factor for disease in the thermally injured patient. With the exception of one study (2), most of these reports are anecdotal or based on seroepidemiological studies (1, 4, 10, 11, 17, 18). In human burn patients, HCMV may potentially be transmitted by skin allografts, as shown by the manifestation of HCMV infection in initially seronegative burn patients grafted with cadaver allografts for temporary wound closure (12). The prevalence of herpesvirus infections (HCMV and herpes simplex virus type 1) in patients with severe burn injuries was estimated to be 52% (10). A significant correlation between herpesvirus infections and bacterial sepsis was found (10), but HCMV or herpes simplex virus type 1 infections did not contribute significantly to the morbidity and mortality of burn patients (1, 10, 11). In contrast, more-detailed data on the immune response of thermally injured mice against murine cytomegalovirus infection have recently become available, showing evidence of a significant contribution of murine cytomegalovirus infection to morbidity and mortality (13–15).

To our knowledge, this is the first case of a productive HCMV infection with documented viral DNAemia and RNAemia in a patient with severe burns. The involvement of the lung could be demonstrated convincingly by the detection of viral DNA, viral RNA, and infectious virus from BAL fluids.

This report demonstrates that HCMV infections in burn patients may well have been underdiagnosed in the past. The self-limited dynamics of viral DNAemia and viral RNAemia may explain several of the former clinical observations and suggest the minor importance of HCMV infection relative to overall mortality. However, the presence of highly productive HCMV replication in the blood and lung of a severely injured burn patient in the context of several septic episodes and prolonged mechanical ventilation warrants further investigation of these findings in a clinical trial, as HCMV reactivation in nonimmunosuppressed critically ill patients with acute sepsis has a high prevalence (9). More-detailed data are necessary to characterize the influence of septic episodes on the dynamics of HCMV replication (6, 7, 16).

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